complex formed between the target molecule and the thiol-containing extender is then used to screen a library of disulfide-containing monophores to identify a library member that has the highest intrinsic binding affinity for a second binding site on the target molecule. LG = leaving group; PG = protecting group; R = reactive group. - -

Please replace paragraph [0034] by the following new paragraph:

- - A "ligand" as defined herein is an entity which has an intrinsic binding affinity for the target. The ligand can be a molecule, or a portion of a molecule which binds the target. The ligands are typically small organic molecules which have an intrinsic binding affinity for the target molecule, but may also be other sequence-specific binding molecules, such as peptides (D-, L- or a mixture of D- and L-), peptidomimetics, complex carbohydrates or other oligomers of individual units or monomers which bind specifically to the target. The term "monophore" is used herein to refer to a monomeric unit of a ligand. The term "diaphore" denotes two monophores covalently linked to each other. The term diaphore is used irrespective of whether the unit is covalently bound to the target or existing separately after its release from the target. The term also includes various derivatives and modifications that are introduced in order to enhance binding to the target. The binding affinity of a diaphore that is higher than the product of the affinities of the individual components is referred to as "avidity." - -

Please replace paragraph [0075] by the following new paragraph:

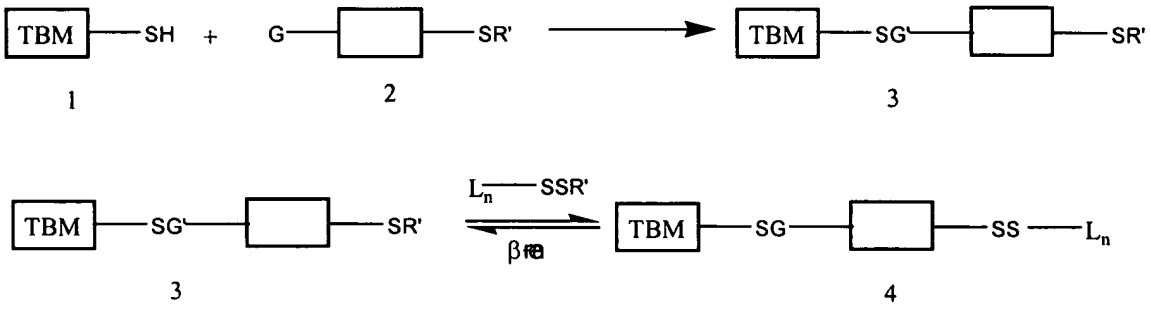
- - It is also preferred that the residue to be mutated to cysteine, or another thiol-containing amino acid residue, not participate in hydrogen-bonding with backbone atoms or, that at most, it interacts with the backbone through only one hydrogen bond. Wild-type residues where the side-chain participates in multiple (>1) hydrogen bonds with other side-chains are also less preferred. Variants for which all standard rotamers (chi1 angle of –60°, 120°, or 180°) can introduce unfavorable steric contacts with the N, CA, C, O, or CB atoms of any other residue are also less preferred. Unfavorable contacts are defined as interatomic distances that are less than 80% of the sum of the van der Waals radii of the participating atoms. - -

Please replace paragraph [0080] by the following new paragraph:

- - Preferred TBM's are proteins and the preferred nucleophiles on the TBM's suitable for forming an irreversible TBM-SME complex include -SH, -OH, $-NH_2$ and –COOH usually arising from side chains of cys, ser or thr, lys and asp or glu respectively. TBM's may be modified (e.g. mutants or derivatives) to contain these nucleophiles or may contain them naturally. For example, cysteine proteases (e.g. Caspases, especially 1, 3, 8 and 9; Cathesepins, especially S and K etc.) and phosphatases (e.g. PTPα, PTP1B, LAR, SHP1,2, PTPβ and CD45) are examples of suitable proteins containing naturally occurring cysteine thiol nucleophiles. Derivatizing such TBM's with a SME to produce a static TBM-SME complex and its reaction with a library member is illustrated below. - -

Please replace the reaction chart on top of page 36 by the following new reaction chart:

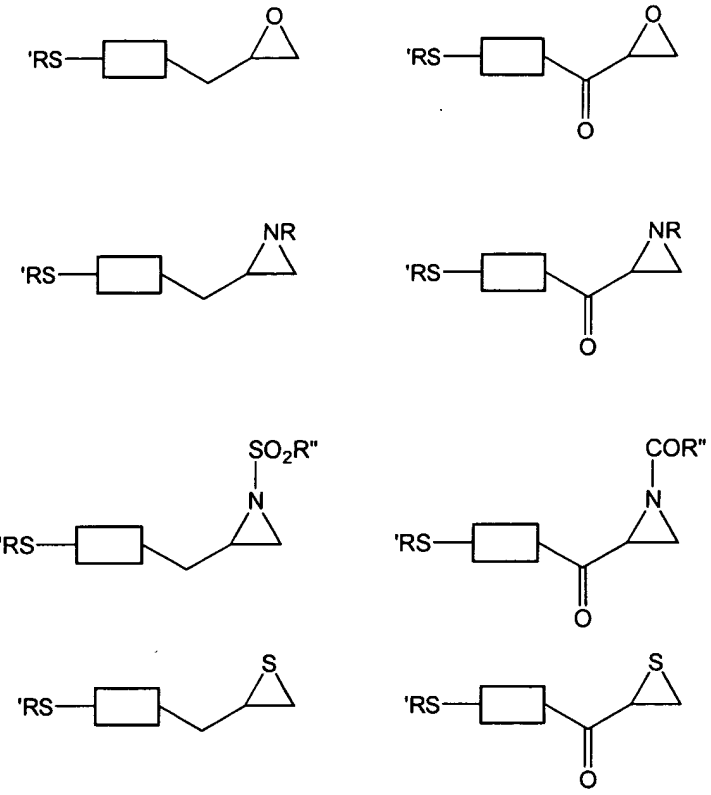
- -



- -

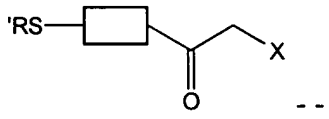
Please replace the structures at the bottom of page 37 and at the top of page 38 by the following new structures:

- -



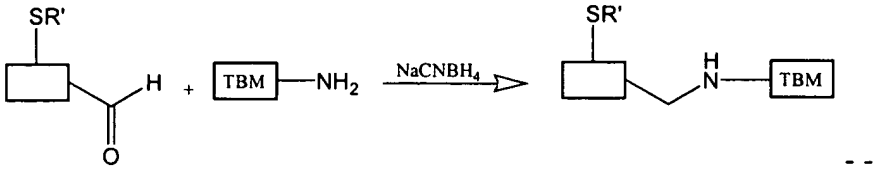
- -

Please replace the structure following paragraph [0085] on page 38 by the following new structure: - -



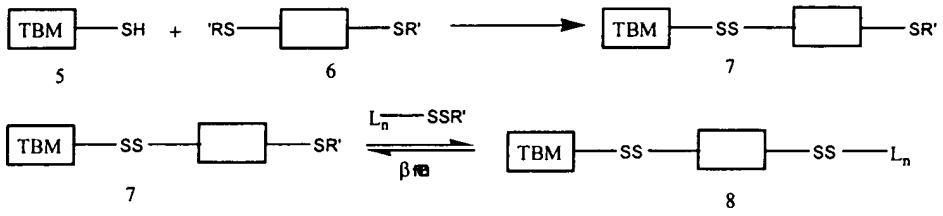
- -

Please replace the chart following paragraph [0088] on page 39 by the following new chart: - -



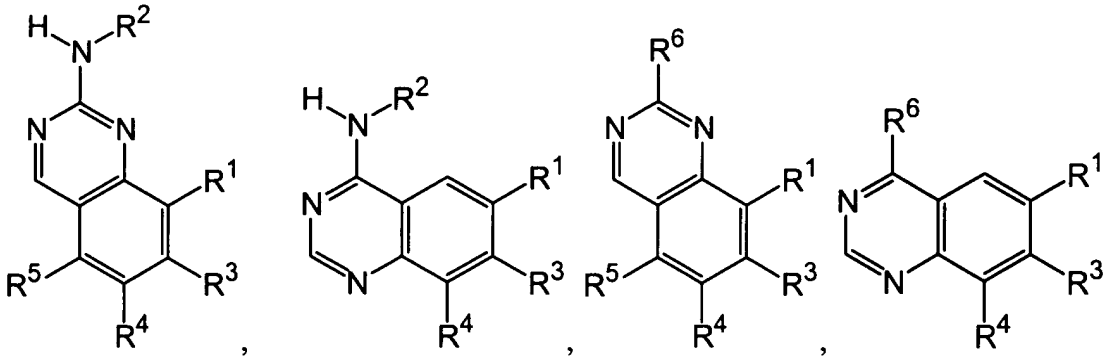
- -

Please replace the chart on the top of page 41 by the following new chart: - -

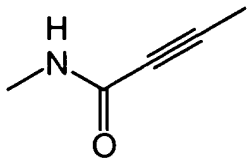
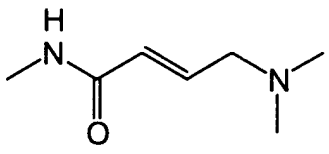
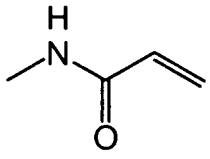


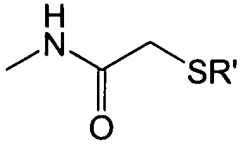
Please replace the first paragraph on top of page 45 by the following new paragraph: - -

SME's are often customized for a particular TBM or family of TBM's. For example quinazoline derivatives are capable of forming static or dynamic extenders with the EGF receptor or an "RD" kinase. In the case of the EGF receptor, cys 773 is a suitable nucleophile for either a static or dynamic quinazoline extender as shown below;



where R^1 is linked to cys 773 through a Michael acceptor or disulfide,

R^1 is selected from  ,  , 

or  ;

R^2 is $-(CH_2)_n$-SR' and $-C(=O)-(CH_2)_n$-SR';

R^3, R^4 and R^5 are $-O-(CH_2)_n$-SR' and $-(CH_2)_n$-SR';

R^6 are; $-(CH_2)_n$-SR'; where n is 1, 2, or 3 and

R' is H, a disulfide or a thiol protecting group. - -

Please replace paragraph [0104] by the following new paragraph:

- - Phosphotyrosine (P-tyr), phosphoserine (P-ser) and phoshpothreonine (P-thr) mimetics or surrogates may be used as extenders in the present invention to identify fragments that interact with subsites nearby to improve specificity or affinity for a target phosphatase. Thus extended tethering using known substrates or inhibitors as "anchors" to find nearby fragments by standard covalent tethering with the extender is one preferred embodiment of the instant invention. - -

Please replace paragraph [0105] by the following new paragraph:

- - Phosphotyrosine (P-tyr) mimetics are examples of SME's that may be customized for phosphatases like PTP-1B, LAR etc. Known PTP-1B P-tyr mimetics derivitized with mercapto-propanoic acid and/or cysteamine or the protected forms thereof, shown below, bind to the active site of a PTP-1B cys mutant. - -

Remarks

The foregoing amendments serve to correct certain errors of formal nature, and do not add new matter. Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached pages are captioned "**Version with markings to show changes made.**:

Applicants respectfully request the examination of this application, and an early issuance of a Notice of Allowance.